General

Guideline Title

Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society.

Bibliographic Source(s)

Chou R, Cruciani RA, Fiellin DA, Compton P, Farrar JT, Haigney MC, Inturrisi C, Knight JR, Otis-Green S, Marcus SM, Mehta D, Meyer MC, Portenoy R, Savage S, Strain E, Walsh S, Zeltzer L, American Pain Society, Heart Rhythm Society. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. J Pain. 2014 Apr;15(4):321-37. PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- March 22, 2016 – Opioid pain medicines : The U.S. Food and Drug Administration (FDA) is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. They are requiring changes to the labels of all opioid drugs to warn about these risks.

Recommendations

Major Recommendations

Quality of evidence (high, moderate, low, insufficient) and strength of recommendation (strong, weak) ratings are provided at the end of the "Major Recommendations" field.

Patient Assessment and Selection

When considering initiation of methadone, the panel recommends that clinicians perform an individualized medical and behavioral risk evaluation to assess risks and benefits of methadone, given methadone's specific pharmacologic properties and adverse effect profile (strong recommendation, low-quality evidence).

Patient Education and Counseling

The panel recommends that clinicians educate and counsel patients prior to the first prescription of methadone about the indications for treatment and goals of therapy, availability of alternative therapies, and specific plans for monitoring therapy, adjusting doses, potential adverse effects associated with methadone, and methods for reducing the risk of potential adverse effects and managing them (strong recommendation, low-quality evidence).

Baseline Electrocardiograms

- The panel recommends that clinicians *obtain* an electrocardiogram (ECG) prior to initiation of methadone in patients with risk factors for corrected electrocardiographic QT (QTc) interval prolongation, any prior ECG demonstrating a QTc >450 ms, or a history suggestive of prior ventricular arrhythmia. An ECG within the past 3 months with a QTc <450 ms in patients without new risk factors for QTc interval prolongation can be used for the baseline study (strong recommendation, low-quality evidence).
- The panel recommends that clinicians *consider* obtaining an ECG prior to initiation of methadone in patients not known to be at higher risk for QTc interval prolongation; an ECG within the past year with a QTc <450 ms in patients without new risk factors for QTc interval prolongation can be used for the baseline study (weak recommendation, low-quality evidence).
- The panel recommends against use of methadone in patients with a baseline QTc interval >500 ms (strong recommendation, low-quality evidence).
- The panel recommends that clinicians consider alternate opioids in patients with a baseline QTc interval ≥450 ms but <500 ms. If methadone is considered in a patient with a baseline QTc interval ≥450 ms but <500 ms, the clinician should evaluate for and correct reversible causes of QTc interval prolongation before initiating methadone (weak recommendation, low-quality evidence).
- The panel recommends that clinicians consider buprenorphine as a treatment option for patients treated for opioid addiction who have risk factors for or known QTc interval prolongation when an agonist/partial agonist is indicated (weak recommendation, moderate-quality evidence).

Initiation of Methadone

The panel recommends that clinicians initiate methadone at low doses individualized based on the indication for treatment and prior opioid exposure status, titrate doses slowly, and monitor patients for sedation (strong recommendation, moderate-quality evidence).

Practice Advice: Based on limited research evidence and clinical experience, the panel suggests the following parameters:

1. When used to treat opioid addiction, the panel suggests that clinicians start methadone at no more than 30 to 40 mg once daily. The dose should be titrated based on objective signs of withdrawal and self-reported craving and methadone dose increased by no more than 10 mg/d and no more frequently than every 3 to 4 days. Methadone should be withheld if there is evidence of sedation.
2. When used to treat chronic pain in adults on relatively low doses of other opioids (e.g., <40 to 60 mg/d of morphine or equivalent), the panel suggests that clinicians start methadone at 2.5 mg three times a day (tid), with initial dose increases of no more than 5 mg/d every 5 to 7 days. In children, the recommended starting dose is 100 µg/kg (maximum 5 mg/dose) every 6 to 8 hours. Methadone should be withheld if there is evidence of sedation.
3. When used to treat chronic pain and switching to methadone from higher doses of another opioid, the panel suggests that clinicians start methadone therapy at a dose 75% to 90% less than the calculated equianalgesic dose and at no higher than 30 to 40 mg/d, with initial dose increases of no more than 10 mg/d every 5 to 7 days. Methadone should be withheld if there is evidence of sedation.

The panel recommends that clinicians consider those patients previously prescribed methadone, but who have not currently taken opioids for 1 to 2 weeks, opioid-naïve for the purpose of methadone reinitiation (strong recommendation, low-quality evidence).

Follow-up Electrocardiograms

- The panel recommends that for patients prescribed methadone, clinicians perform follow-up ECGs based on baseline ECG findings, methadone dose changes, and other risk factors for QTc interval prolongation (strong recommendation, low-quality evidence).
  Practice Advice: Based on limited research evidence and based upon clinical experience, the panel suggests the following parameters:

1. The panel suggests that for patients with risk factors for QTc interval prolongation, any prior ECG demonstrating a QTc >450 ms, or a history of syncope, clinicians perform follow-up ECG 2 to 4 weeks after initiation of methadone therapy and following significant dose increases.
2. The panel suggests that for all patients, clinicians perform follow-up ECG when the methadone dose reaches 30 to 40 mg/d in patients started at lower doses, and again at 100 mg/d.
3. The panel suggests that clinicians perform follow-up ECG for all patients prescribed methadone with new risk factors for QTc interval prolongation or signs or symptoms suggesting arrhythmia.

- The panel recommends that clinicians switch methadone-treated adults with a QTc interval ≥500 ms to an alternative opioid or immediately reduce the methadone dose; in all such cases, the panel recommends that clinicians evaluate and correct reversible causes of QTc interval prolongation, and repeat the ECG after the methadone dose has been decreased (strong recommendation, low-quality evidence).
- The panel recommends that clinicians consider switching methadone-treated adults with a QTc interval ≥450 ms but <500 ms to an alternative opioid or reducing the methadone dose. In patients in whom there are barriers to switching to alternative opioids, or who experience decreased treatment effectiveness with methadone dose reductions, the panel recommends that clinicians discuss with patients the potential risks of continued methadone. In all cases, the panel recommends that clinicians evaluate and correct reversible causes of QTc interval prolongation, and repeat the ECG after the methadone dose has been decreased (strong recommendation, low-quality evidence).

Monitoring for and Management of Adverse Events

- The panel recommends that patients receiving methadone be monitored for common opioid adverse effects and toxicities and that adverse effects management be considered part of routine therapy (strong recommendation, moderate-quality evidence).
- The panel recommends face-to-face or phone assessment with patients to assess for adverse events within 3 to 5 days after initiating methadone, and within 3 to 5 days after each dose increase (strong recommendation, low-quality evidence).

Urine Drug Testing

- The panel recommends that clinicians obtain urine drug screens prior to initiating methadone and at regular intervals in patients prescribed methadone for opioid addiction (strong recommendation, low-quality evidence).
- The panel recommends that patients prescribed methadone for chronic pain who have risk factors for drug abuse undergo urine drug testing prior to initiating methadone and at regular intervals thereafter; it recommends that clinicians consider urine drug testing in all patients regardless of assessed risk status (strong recommendation, low-quality evidence).

Medication Interactions

The panel recommends that clinicians use methadone with care in patients using concomitant medications with potentially additive side effects or pharmacokinetic or pharmacodynamic interactions with methadone (strong recommendation, low-quality evidence).

Methadone Use in Pregnancy

The panel recommends monitoring of neonates born to mothers receiving methadone for neonatal abstinence syndrome and treatment for neonatal abstinence syndrome when present (strong recommendation, moderate-quality evidence).

Definitions

Each recommendation received a separate grade for the strength of the recommendation (strong or weak) and for the quality of evidence (high, moderate, or low).

American Pain Society Clinical Practice Guidelines Grading System*

	Strength of Recommendation	
Quality of Evidence	Benefits Do or Do Not Clearly Outweigh Risks	Benefits and Risks and Burdens Are Finely Balanced
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits	No recommendation	No recommendation

or harms	Strength of Recommendation	
Quality of Evidence	Benefits Do or Do Not Clearly Outweigh Risks	Benefits and Risks and Burdens Are Finely Balanced

*From the system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Work Group and adapted by the American Pain Society.

Quality of Evidence

The strength of evidence for each key question was rated using the four categories recommended in the Agency for Healthcare Research and Quality (AHRQ) guide (see the "Rating Scheme for the Strength of the Evidence field" for a full description of this process): A "high" grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change confidence in the estimate of effect; a "moderate" grade indicates moderate confidence that the evidence reflects the true effect and further research may change confidence in the estimate of effect and may change the estimate; a "low" grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate; an "insufficient" grade indicates evidence either is unavailable or does not permit a conclusion.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Chronic pain
- Opioid addiction

Guideline Category

Counseling

Evaluation

Management

Risk Assessment

Treatment

Clinical Specialty

Cardiology

Family Practice

Internal Medicine

Obstetrics and Gynecology

Oncology

Pediatrics

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Physician Assistants

Physicians

Social Workers

Substance Use Disorders Treatment Providers

Guideline Objective(s)

To provide, where possible, evidence-based recommendations for use of methadone in persons of all ages (including pregnant women) for treatment of chronic pain in primary care or specialty settings or for treatment of opioid addiction in licensed opioid treatment programs

Target Population

Persons of all ages (including pregnant women) receiving methadone for treatment of chronic pain in primary care or specialty settings or for treatment of opioid addiction in licensed opioid treatment programs

Interventions and Practices Considered

1. Individualized medical and behavioral risk evaluation to assess risks and benefits of methadone
2. Educating and counseling patients on methadone therapy including potential for adverse effects
3. Baseline electrocardiogram (ECG) to identify persons at greater risk for methadone-associated arrhythmia
4. Use of alternative opioids in patients at high risk of complications related to corrected electrocardiographic QT (QTc) interval prolongation
5. Careful dose initiation and titration of methadone
6. Follow-up ECG
7. Diligent monitoring for and management of adverse events
8. Urine drug screens prior to initiating methadone and at regular intervals
9. Consideration of medication interactions in patients using concomitant medications
10. Monitoring of neonates born to mothers receiving methadone for neonatal abstinence syndrome

Major Outcomes Considered

- Overdose
- Mortality (including sudden death)
- Discontinuation due to adverse events
- Syncope
- QT prolongation
- Torsades de pointes/arrhythmias
- Endocrinologic/bone density/immunologic effects
- Pregnancy outcomes
- Neonatal withdrawal
- Constipation/gastrointestinal adverse effects
- Cognitive functioning/other psychiatric disorders
- Respiratory depression/sleep apnea
- Abuse/addiction/hyperalgesia

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note: This Guideline is informed by a systematic evidence review that addressed a variety of topics related to methadone safety conducted at the Oregon Evidence-based Practice Center and commissioned by the American Pain Society (APS) and the College on Problems of Drug Dependence (CPDD) (see the "Availability of Companion Documents" field).

With the Oregon Evidence-based Practice Center, the panel developed the key questions, scope, and inclusion criteria used to guide the evidence review.

Literature Search and Strategy

Oregon Evidence-based Practice Center staff searched the Cochrane Library, Ovid® MEDLINE, and PsycINFO through July 2012 for studies assessing harms associated with methadone use (detailed search strategies are shown in Appendix C of the systematic review). An update search was performed in January 2014 for new studies on methadone-related overdose and arrhythmia. Reviews of reference lists supplemented the electronic searches.

Inclusion and Exclusion Criteria

All identified citations were imported into an electronic database (EndNote® X1) and reviewed for inclusion. One investigator reviewed potential citations for inclusion and a second investigator checked excluded citations to identify potentially relevant citations not selected by the first reviewer. Review staff included studies that met all of the following criteria:

- Evaluated children or adults prescribed oral or intravenous methadone or infants whose mothers were methadone users
- Were relevant to a key question
- Reported harms associated with methadone use
- For all key questions and harms: Were systematic reviews, randomized or quasi-randomized trials, cohort studies, cross-sectional studies, or case-control studies
- For mortality, overdose, cardiac events, electrocardiographic changes, and pregnancy-related harms, as well as for key questions that addressed risk factors for methadone-associated harms: review staff also included prevalence studies, before-after studies, and case series.

Studies only published as conference abstracts were excluded. Non-English language studies were excluded. Other reviews, policy statements, and articles without original data were obtained for background and contextual information, but were not included as evidence.

Number of Source Documents

Investigators reviewed 3,750 potentially relevant citations. Of these, 1,107 full-text articles were retrieved to review for inclusion. After review of full-text articles, 161 studies were judged to be relevant to one or more key questions and to meet inclusion criteria. The most common reasons for study exclusion were: wrong outcomes (did not address included harms); wrong study design (pharmacokinetics, case reports, pharmacodynamics); and wrong publication type (editorial, opinion, letters, guidelines, narrative, or non-systematic review).

Two systematic reviews and 169 primary studies that were relevant for at least one key question were identified and met inclusion criteria. These included 34 randomized trials (four of which were included in one of the systematic reviews), 108 observational studies (in 111 publications) and 27 case series.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

The strength of evidence for each key question was rated using the four categories recommended in the Agency for Healthcare Research and Quality (AHRQ) guide: A "high" grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change confidence in the estimate of effect; a "moderate" grade indicates moderate confidence that the evidence reflects the true effect and further research may change confidence in the estimate of effect and may change the estimate; a "low" grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate; an "insufficient" grade indicates evidence either is unavailable or does not permit a conclusion.

See the "Rating of a Body of Evidence" section in the original guideline document for additional explanation.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note: This Guideline is informed by a systematic evidence review that addressed a variety of topics related to methadone safety conducted at the Oregon Evidence-based Practice Center and commissioned by the American Pain Society (APS) and the College on Problems of Drug Dependence (CPDD) (see the "Availability of Companion Documents" field).

Data Extraction and Synthesis

Randomized Trials

For randomized trials, the reviewers abstracted the following information:

- Inclusion and exclusion criteria
- Number of patients enrolled
- Demographics and baseline characteristics
- Setting
- Funding source
- Interventions evaluated
- Duration of follow-up
- Loss to follow-up
- Compliance to treatment
- Adverse events

The internal validity (quality) of randomized clinical trials was assessed using 11 predefined criteria developed by the Cochrane Back Review Group (see Appendix D of the systematic review for details on how reviewers operationalized the criteria). The reviewers rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; the use of co-interventions; compliance to allocated therapy; adequate reporting of dropouts and loss to follow-up; degree of loss to follow-up; non-differential timing of outcome assessment; and the use of intention-to-treat analysis.

An overall quality grade was assigned based on the type, number and seriousness of methodological flaws. The reviewers graded trials with no or only minor flaws good-quality, those with serious flaws poor-quality, and all others fair-quality, as described in further detail below.

Studies rated "good" have the least risk of bias and results are considered valid. Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates, and clear reporting of dropouts; appropriate means for preventing bias; appropriate measurement of outcomes, and reporting results.

Studies rated "fair" are susceptible to some bias, but it is not sufficient to invalidate the results. These studies do not meet all the criteria for a rating of good-quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The "fair" quality category is broad, and studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are likely to be valid, while others are only probably valid.

Studies rated "poor" have significant flaws that imply biases of various types that may invalidate the results. They have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting. The results of these studies are at least as likely to reflect flaws in the study design as the true difference between the compared medications. Reviewers did not exclude studies rated poor-quality a priori, but poor-quality studies were considered to be less reliable than higher quality studies when synthesizing the evidence, particularly when discrepancies between studies were present.

Observational Studies

For observational studies, the reviewers abstracted the following information:

- Study design (cohort, case-control, cross-sectional, before-after, case series, prevalence, or other)
- Inclusion and exclusion criteria
- Number of patients eligible and included
- Demographics and baseline characteristics
- Country and setting
- Funding source
- Interventions evaluated
- Duration of follow-up (for studies using a longitudinal design)
- Loss to follow-up (for studies using a longitudinal design) or proportion of patients meeting inclusion criteria who were analyzed
- Adverse events

The internal validity (quality) of observational studies was assessed using predefined criteria based on those developed by Downs and Black and the US Preventive Services Task Force (see Appendix D in the systematic review). The internal validity of each study was rated based on the methods used to select patients for inclusion (ideally, enrollment of consecutive or a random sample patients meeting inclusion criteria, with matching if appropriate for the study design); similarity of compared groups at baseline (for comparative studies); accuracy of methods for ascertaining exposures, confounders, and outcomes; blinding of outcomes assessors; adequate reporting of drop-outs (for longitudinal studies) or the proportion of patients meeting inclusion criteria who were analyzed (for non-longitudinal studies); degree of loss to follow-up or proportion meeting inclusion criteria who were analyzed; and statistical analyses on potential confounders. As with randomized trials, an overall quality grade was assigned based on the type, number and seriousness of methodological flaws (see above). Reviewers graded studies with no or only minor flaws good-quality, those with serious flaws poor-quality, and all others fair-quality.

In general, a good-quality observational study is considered less reliable than a good-quality randomized trial. Among the observational studies, evidence hierarchies typically place a good-cohort study at the top, followed by case-control studies, cross-sectional studies, before-after studies, and other uncontrolled studies (e.g., case series and prevalence studies).

Systematic Reviews

The reviewers included recent, higher-quality systematic reviews on mortality risk associated with use of methadone. Systematic reviews were defined as studies that at a minimum described systematic methods for identifying and selecting studies and synthesizing evidence. For each systematic review, reviewers abstracted the following information:

- Databases searched
- Dates of the searches
- Language restrictions, if any
- Number of studies included
- Criteria used to include studies
- Limitations of the included studies
- Methods for rating the quality of included studies
- Methods for synthesizing the evidence
- Interventions evaluated
- Number of treatment and control subjects
- Adverse event outcomes (including number and quality of studies for each comparison and outcome, and pooled results if available)

The reliability of systematic reviews depends on how well they are conducted. Predefined criteria adapted from the Assessment of Multiple Systematic Reviews (AMSTAR) tool were used to assess the internal validity of systematic reviews (see Appendix D in the systematic review). Each study was evaluated on the following criteria: comprehensiveness of search strategy, application of pre-defined inclusion criteria to select studies, dual selection of studies, dual extraction of data, adequate explanation of included studies, appropriate assessment of validity and use of appropriate methods to synthesize the evidence. Reviewers assigned an overall quality grade based on the type, number and seriousness of methodological flaws. Systematic reviews with major flaws are more likely to produce positive conclusions about the effectiveness of interventions. Reviewers graded systematic reviews with no or only minor flaws good-quality, those with serious flaws poor-quality, and all others fair-quality.

Dual Review

Two reviewers independently rated the quality of each systematic review and primary study. Discrepancies were resolved via a consensus process.

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

Panel Composition

The American Pain Society (APS) and the College on Problems of Drug Dependence (CPDD) convened a panel of 16 members with expertise in pain, addiction medicine, cardiology, primary care, nursing, palliative care, pharmacology, adolescent medicine, obstetrics and gynecology, epidemiology, and social work to review the evidence and formulate recommendations on methadone safety. Two cochairs were selected by the APS and CPDD to lead the panel, which also included the APS Director of Clinical Guidelines Development. The Heart Rhythm Society (HRS) was invited to join the guideline development process after cochair and initial panel selection had taken place, and it appointed 2 members with expertise in arrhythmia to the panel.

Guideline Development Process

The Guideline panel met in person in May 2010 and July 2011. At the first meeting, the panel developed the scope and key questions used to guide the systematic evidence review. At the second meeting, the panel reviewed the results of the evidence review and drafted initial potential recommendation statements. Following the second meeting, additional draft recommendation statements were proposed. The panelists then participated in a multistage Delphi process, in which each draft recommendation was ranked on clinical importance and usefulness, and revised. At each stage of the Delphi process, the lowest-ranked recommendations were eliminated. A two-thirds majority was required for a recommendation to be approved. However, unanimous or near-unanimous consensus was achieved for all recommendations. After finalization of the recommendations, the Guideline was written by various panel members and drafts distributed to the panel for feedback and revisions.

Grading of the Evidence and Recommendations

The panel used methods adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group to rate the recommendations included in this Guideline. Each recommendation received a separate grade for the strength of the recommendation (strong or weak) and for the quality of evidence (high, moderate, or low) (see the "Rating Scheme for the Strength of the Recommendations" field). In general, a strong recommendation is based on the panel's assessment that the potential benefits of following the recommendation clearly outweigh potential harms and burdens, or that the potential harms clearly outweigh potential benefits. Given the available evidence, most clinicians and patients would choose to follow a strong recommendation. A weak recommendation is based on the panel's assessment that benefits of following the recommendation outweigh potential harms and burdens (or vice versa), but the balance of benefits to harms or burdens is smaller or evidence is weaker. Decisions to follow a weak recommendation could vary depending on specific clinical circumstances or patient preferences and values. For grading the quality of a body of evidence that supports a recommendation, the panel considered the type, number, size, and quality of studies; strength of associations or effects; and consistency of results among studies. The quality of evidence indicates the level of certainty in the recommendation and the likelihood that future research could change recommendations. A recommendation based on low-quality evidence has a high probability of being affected by new evidence, and a recommendation based on high-quality evidence has a low probability. Strong recommendations based on low-quality evidence indicate that until better evidence becomes available, the panel determined that the benefits of following the recommended course of action clearly outweigh harms. In some cases, recommendations based on low-quality evidence are followed by "practice advice" with more specific suggestions for implementing the recommendation in clinical practice, based on panel consensus.

Rating Scheme for the Strength of the Recommendations

American Pain Society Clinical Practice Guidelines Grading System*

	Strength of Recommendation	
Quality of Evidence	Benefits Do or Do Not Clearly Outweigh Risks	Benefits and Risks and Burdens Are Finely Balanced
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or harms	No recommendation	No recommendation

*From the system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Work Group and adapted by the American Pain Society.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

More than 20 external peer reviewers from multiple clinical and scientific disciplines and professional societies were solicited for additional comments. After another round of revisions and panel approval, the Guideline was approved by the American Pain Society (APS) Board of Directors on May 7, 2013, and by the College on Problems of Drug Dependence (CPDD) Board of Directors on November 5, 2013.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Safer use of methadone and prevention of methadone-associated deaths

Potential Harms

- The pharmacology of methadone may be associated with unique safety concerns. This pharmacology includes a long and variable half-life, potential interactions with multiple medications, variability in equianalgesic dose ratios depending on dose, and association with prolongation of the corrected electrocardiographic QT (QTc) interval, which may predispose patients to the ventricular arrhythmia torsades de pointes.
- Safe use of methadone requires clinical skills and knowledge in use of methadone to mitigate potential risks, including serious risks related to risk of overdose and cardiac arrhythmias.
- In addition to QTc interval prolongation, methadone is associated with other adverse effects typically associated with opioids, including constipation, nausea, sedation, respiratory depression, pruritus, endocrinologic effects, and others.
- Patients treated for opioid addiction are at high risk for opioid abuse and misuse and generally warrant frequent monitoring. Patients prescribed methadone for chronic pain who may need more frequent or intense monitoring include those with a prior history of substance use disorder, patients with an unstable or dysfunctional social environment, and those with comorbid psychiatric conditions.
- Neonatal abstinence syndrome occurs in three quarters or more of infants exposed to methadone prenatally.

Refer to the original guideline document and the systematic evidence review (see the "Availability of Companion Documents" field) for additional discussion of methadone harms.

Contraindications

Contraindications

- Because of its long half-life and variable pharmacokinetics, the panel recommends that methadone not be used to treat breakthrough pain or as an as needed medication.
- The panel suggests that clinicians generally avoid benzodiazepines in patients prescribed methadone because of the possible association with increased overdose risk.

Qualifying Statements

Qualifying Statements

- Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. As part of a shared decision-making approach, it may be appropriate for the clinician to inform a patient that a particular recommendation may not be applicable, after considering all circumstances pertinent to that individual.
- The authors are solely responsible for the content of this article and the decision to submit for publication.
- The Guideline was approved by the American Pain Society (APS) and the College on Problems of Drug Dependence (CPDD), but the content of the Guideline is the responsibility of the authors and panel members.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Resources

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Chou R, Cruciani RA, Fiellin DA, Compton P, Farrar JT, Haigney MC, Inturrisi C, Knight JR, Otis-Green S, Marcus SM, Mehta D, Meyer MC, Portenoy R, Savage S, Strain E, Walsh S, Zeltzer L, American Pain Society, Heart Rhythm Society. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. J Pain. 2014 Apr;15(4):321-37. PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Apr

Guideline Developer(s)

American Pain Society - Professional Association

College on Problems of Drug Dependence - Nonprofit Organization

Source(s) of Funding

Funding for the guideline was provided by the American Pain Society (APS).

Guideline Committee

Expert Panel

Composition of Group That Authored the Guideline

Panel Members: Roger Chou, Departments of Medicine and Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, and Pacific Northwest Evidence-based Practice Center, Portland, Oregon; Ricardo A. Cruciani (*Panel Co-chair*), Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, New York; David A. Fiellin (*Panel Co-chair*), School of Public Health, Department of Medicine, Yale School of Medicine, New Haven, Connecticut; Peggy Compton, UCLA School of Nursing, Los Angeles, California; John T. Farrar, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, Pennsylvania; Mark C. Haigney, Cardiology Uniformed Services, University of the Health Sciences, Baltimore, Maryland; Charles Inturrisi, Department of Pharmacology, Weill Cornell Medical College, New York, New York; John R. Knight, Center for Adolescent Substance Abuse Research, Children's Hospital Boston, Boston, Massachusetts; Shirley Otis-Green, Division of Nursing Research and Education, Department of Population Sciences, City of Hope National Medical Center, Duarte, California; Steven M. Marcus, School of Biomedical and Health Sciences, New Jersey Medical School, Rutgers University, Newark, New Jersey; Davendra Mehta, Departments of Medicine and Cardiology, Icahn School of Medicine at Mount Sinai, New York, New York; Marjorie C. Meyer, Departments of Gynecology and Maternal Fetal Medicine, University of Vermont, Burlington, Vermont; Russell Portenoy, Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, New York; Seddon Savage, Department of Anesthesiology, Dartmouth Medical School, Hanover, New Hampshire; Eric Strain, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland; Sharon Walsh, Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky College of Medicine, Lexington, Kentucky; Lonnie Zeltzer, Pediatric Pain Program, Mattel Children's Hospital at UCLA, Los Angeles, California

Financial Disclosures/Conflicts of Interest

All panelists were required to disclose conflicts of interest within the preceding 5 years at all face-to-face meetings and prior to submission of the Guideline for publication, and to recuse themselves from votes if a conflict was present. A list of authors with disclosed conflicts of interest is shown in Appendix 1 in the original guideline document.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the Journal of Pain Web site .

Availability of Companion Documents

The following are available:

- Chou R, Weimer M, Dana T, Walker M, Mitchell JP. Systematic evidence review on methadone harms and comparative harms. Chicago (IL): American Pain Society; 2014. 327 p. Electronic copies: Available from the American Pain Society (APS) Web site .
- The methadone safety guidelines: a live webinar. Chicago (IL): American Pain Society; 2014 Nov 11. 54 p. Available as a webinar or slide set from the APS Web site.
- The methadone safety guidelines: a live webinar Q&A. Chicago (IL): American Pain Society; 2014 Nov 11. 4 p. Electronic copies: Available from the APS Web site .

Patient Resources

None available

NGC Status

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